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Altered microstructural connectivity of the arcuate fasciculus is related to language disability in children with autism spectrum disorder

（学童期自閉症における言語機能と弓状束の microstructural connectivity に関する検討）

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Abstract

Autism spectrum disorder (ASD) is a neuro-developmental disorder characterized by a number of functional abnormalities including disruptions to language. Recently, abnormal connectivity in the brain has been reported as a neuronal basis of functional impairments in ASD. Using tractographical analysis of the arcuate fasciculus (AF) by Diffusion Tensor Imaging (DTI), we attempted to clarify the neuropsychological basis for the language impairment in ASD by investigating thirteen school-aged children with ASD and eleven age- and IQ-matched control subjects. As a result of the DTI examination, no statistically significant differences in the values of fractional anisotropy (FA), axial diffusivity, radial diffusivity, and mean diffusivity were found. In both TD and ASD groups, the FA score of the AF was higher in the left hemisphere than it was in the right. We revealed that in children with ASD, the FA values of the left AF showed a positive correlation between age, verbal intelligence quotient (VIQ), and full-scale intelligence quotient (FSIQ). In addition, a negative correlation was found between RD values on the left AF with VIQ, FSIQ, and age in children with ASD. This is the first report to reveal a correlation between microconnectivity of the AF and VIQ in children diagnosed with ASD. Therefore, these findings suggest that the altered microstructural integrity of the AF may be related to verbal ability in ASD.

Introduction

Autism spectrum disorder (ASD) is a complex group of neurodevelopmental disorders characterized by deficits in a wide range of social communication and social interaction across multiple contexts, such as deficits in social-emotional reciprocity, nonverbal communicative behaviors used for social interaction, and developing, maintaining, and understanding relationships; as well as by restricted and repetitive patterns of behavior, interests, and/or activities [1].

Recently, many studies have revealed the altered connectivity within the brain of patients with ASD [2, 3]. The most commonly used and non-invasive method to measure such connectivity is magnetic resonance diffusion tensor imaging (DTI). Main DTI parameters consist of fractional anisotropy (FA), axial diffusivity (AD), mean diffusivity (MD), and radial diffusivity (RD). FA is sensitive to myelination, axon diameter, fiber density, and fiber coherence, and thus FA is thought to represent microstructural integrity of white matter [4, 5]. In healthy children, FA values increase in a region-specific manner in the brain and are related to childhood cognitive achievement [6, 7]. Several human and animal studies have suggested that AD is related to axonal integrity, and RD to alterations associated with myelination [8, 9]. Moreover, many studies have reported significant differences in FA of the superior longitudinal fasciculus (SLF) [10-17], corpus callosum [18], uncinate fasciculus [19],

inferior longitudinal fasciculus [16], and superior cerebeller peduncles [20] as well as increased or decreased AD, MD, and RD values in these brain regions of ASD groups as compared to control groups.

Subjects with ASD often show functional abnormalities in the use of language. More specifically, syntactic and pragmatic impairments have been recently identified to be associated with ASD [21, 22]. Broca's area in the inferior frontal gyrus (IFG), Wernick's area in the posterior superior temporal gyrus (STG), and Geschwind's area in the inferior parietal lobule have been shown as the classical cortical language regions [23, 24]. It was reported that those with ASD tend to have asymmetrical volumes in Broca's area or STG areas [25], and that volume of both gray- and white matter is increased in the right IFG in ASD [26] when compared to controls. By means of voxel-based morphometry, gray matter volume is reported to decrease in both sides of the superior temporal sulcus (STS) in subjects with ASD [27]. There are many data about anatomical differences between ASD and TD, but they are still under debate.

The arcuate fasciculus (AF) is the white matter fiber bundle, which connects the classical cortical language regions described above. López-Barroso *et al.* reported that performance in word learning correlates with microstructural properties and strength of functional connectivity of the direct connections between Broca's and Wernicke's territories in the left

hemisphere [28]. AF is thus considered to be crucial to the function of language usage.

DTI studies investigating AF have reported significant reduction of FA score [11, 12, 15, 16], and significant increases in AD, MD, and RD scores in subjects with ASD [10, 29]. However, significant increases in FA scores in young children with ASD have also been observed [14]. In addition, Brito et al. [30] revealed no difference in the SLF, of which the AF is a part, between TD and ASD populations (Table 1). These findings suggest that microstructural abnormalities exist in the AF of patients with ASD and that these abnormalities change during development.

In this study, we investigated the relationship between AF and language function in school-aged children with ASD in order to clarify the neuropsychological basis of language impairment in subjects with ASD.

Participants

Participants included 13 children diagnosed with ASD (12 males and one female; mean age: 9.70±2.72 years; range: 5-14 years) and 11 typically developing (TD) children (10 males and one female; mean age: 10.50±2.11 years; range: 7-13 years). The diagnosis of ASD was based on the Diagnostic and Statistical Manual of Mental Disorders-4th Edition-Text Revision [31] criteria, and the Autism Diagnostic Observation Schedule-Generic

(ADOS-G) [32]. None of the subjects with ASD had a history of seizures. Two patients with

ASD were on medication with either methylphenidate or atomoxetine. In TD groups, the

presence of ASD was rule out based on the Japanese version of the Autism Screening

Questionnaire (ASQ-J). Participants in the TD group all denied personal and family histories

of ASD, as well as any other neurological/psychiatric conditions. In the Edinburgh

Handedness Inventory [33], all participants were right-handed. The Wechsler intelligence

Scale for Children, Third Edition (WISC-III) was used for the evaluation of overall cognition.

The two groups were matched on age, full Scale Intelligence quotient (FSIQ), verbal

intelligence quotient (VIQ), and handedness (Table 2). We chose an IQ threshold of > 80 to

ensure normal intelligence and thus to minimize the effect of IQ on verbal assessment.

In order to acquire MRI data, sedation was required in two children with ASD. This study

was approved by the Institutional Review Board of Osaka University Hospital. Written

informed assent and consent was obtained from the parents of all participants.

MRI acquisition

Diffusion tensor (DT) images were acquired on a 3 tesla GE MR system (Signa Excite HD;

GE Healthcare, Milwaukee, USA). DTI was performed using single-shot spin-echo

echo-planar imaging with sensitivity-encoding parallel imaging (undersampling factor of two).

Diffusion-weighted images were acquired in the axial plane with six non-collinear directions. Imaging parameters were as follows: TR=12,000ms; TE=86ms; FOV=260×260mm^2; matrix size=128irec voxels; slice thickness=3mm; slice gap=0; number of slices=45-48; NEX=1; and diffusion-weighting factor b= 800 and 0 s/mm^2. Foam pillows and cushions were used to minimize participants' head movements.

DTI data analysis

The diffusion data were preprocessed using DtiStudio software (www.mristudio.org). Using DtiStudio, we first corrected the diffusion data for eddy current and head motion artifacts by the Automatic Image Registration (AIR) program. Diffusion-weighted images were then realigned to the b=0 image using a 12-parameter affine registration.

Tractography approach

Tensor calculation and tractography used the DtiStudio. Tractography was demonstrated on the basis of the Fiber Assignment by Continuous Tracking (FACT) method [34]. Tracking was performed first from all pixels inside the brain by using the brute-force approach. Then, a multiple-ROI approach was used to reconstruct all tracts of interest. To reconstruct AF pathways, a FA and a turning angle threshold for the termination of fiber tracking were set to

0.20 and 60 degrees based on previous publications (Figure 1) [35]. The AF was identified on

the DTI color map. The first ROI was placed in the coronal plane at the level of the posterior

tip of the putamen using the "OR" operator lateral to the superior aspect of the corona

radiate [36]. The whole AF was created by the additional "AND" operations. Furthermore,

aberrant fibers that did not correspond to the known anatomic location were occasionally

removed using a "NOT" operator. The AF could be discretely identified, and the trajectory

of the AF was checked by previously published white matter atlases [37]. The reconstructed

AF is represented in Figure 1.

DTI outcome measurements

The FA, AD, RD, and MD values obtained in the AF were used for comparison between

patients with autism and controls. Tractograpy was performed by two raters (MK and IM).

Statistical analysis

Statistical analysis was performed using SPSS (IBM Inc., Tokyo, Japan). Age, IQ, and

handedness were compared by independent sample t-tests. The DTI outcome

measurements used repeated-measures analysis of variance (ANOVA) with side (left/right)

as the within-subject factor and group (ASD/TD) as the between-subjects factor. The effect

of age, VIQ, PIQ, and FSIQ on the measured FA, AD, RD, and MD on both the right and left

hemispheres was examined individually using Pearson correlations.

Results

Demographics

Demographic date is shown in Table 2. There were no significant differences between the

two groups in age, FSIQ, VIQ, or handedness (Table 1). Performance intelligent quotient

(PIQ) was significantly higher in the TD group.

3.2 Group differences in DTI outcome measurements

DTI outcome measurements are shown in Table 3. There were no significant differences

between the ASD group and TD group in DTI outcome measurements of the AF. The MD

($p<0.001$) and RD ($p<0.01$) were higher in the right hemisphere than in the left hemisphere

in both TD and ASD groups (Table 3).

3.2 The relationships between age, VIQ, PIQ, and FSIQ and DTI outcome measures

We performed correlation analysis between age, VIQ, PIQ, and FSIQ and DTI outcome

measures. AD and MD were negatively correlated with age and FIQ in TD but not in ASD

(data not shown). There were significant correlations between FA and RD values and age, VIQ, and FSIQ. The relationship between FA in the left AF and age, VIQ, and FSIQ in ASD and TD is shown in Figure 1. A significant positive correlation between FA in the left AF and age (r=0.828; p<0.001), FSIQ (r=0.748; p<0.001), and VIQ (r=0.572; p<0,005) were observed only in the ASD group. Similarly, a significant negative correlation was observed between RD values in the left AF and age (r=-0.851; p<0.001), FSIQ (r=-0.580; p<0.005), and VIQ (r=-0.580; <0.005) only in the ASD group.

Discussion

We investigated microstructures of AF in school-aged children with ASD and TD using DTI tractography. We found that the FA and RD values of the AF correlated with VIQ in school-aged children with ASD. To the best of our knowledge, this is the first report about altered microstructural connectivity of the AF as it is related to language impairments in children with ASD.

In ASD, the FA positively correlated and RD negatively correlated with age, FSIQ, and VIQ. Moreover, we discovered that FA was influenced a great deal by RD, MD, or AD [38]. In our results, AD and MD, which reflected the number of axons and axonal diameter [39], revealed no correlation between age, VIQ, or FSIQ (data not shown). These results suggest that RD,

which reflects the alteration of myelination, may contribute to the FA level in school-aged children with ASD in terms of the AF.

There was no significant difference in the values of FA, AD, MD, RD, and fiver volume of AF between the ASD and TD participants of this age group. This result is consistent with previous reports [40]. On the other hand, Groen et al. reported that school-aged boys and adults with ASD showed declined values of FA [15], while the values of MD, RD, and AD tended to increase [11, 17]. Some studies specifically targeting children reported that FA values were higher among children with ASD in comparison with TD controls [14]. Thus, these data are still controversial; however, considering the variable language functioning in each patient with ASD, we should take into account the functional level corresponding to the brain region in question.

Regarding AF, there have been several reports that have revealed its laterality: larger volumes and higher FA values have been reported in the left AF of healthy control adults [41], whereas FA values were observed to be less lateralized in adolescents with ASD [10]. A significant negative correlation between RD lateralization and language function was also reported [10]. In the current study, we revealed that MD and RD values were significantly higher in the right- versus the left AF of children with ASD and that the RD value in the left side of the AF was correlated with verbal function in school-aged children with ASD. The

reason for the inconsistency between reports remains unknown, however, the age of children in our study was younger than in Fletcher's report. Song et al. reported that myelination contributes to the level of RD [42, 43], and that it actively progresses during early childhood. Thus, it could be that the impaired or delayed development of left-dominant laterality of children with ASD observed in our study may in part be due to the delayed maturation of myelin.

In the TD group, MD and AD negatively correlated with age and FIQ. These data may indicate that axonal development was still ongoing in TD during the ages that we observed in the current study. FA and RD were not significantly correlated with age, VIQ, and FSIQ. Weinstein et al. revealed that FA value changes between the age of 0.5 and 5.8 years in children with TD and ASD [14], and that FA is higher in ASD than TD throughout this period. This suggests that microconnectivity is maturing at least until five years in TD children. In our study, we found that the FA value remained constant in the TD group in ages ranging from seven to 14 years, thus, microconnectivity of the FA was largely matured as early as seven years in TD children. On the other hand, between FA and age, a positive correlation in the ASD group was still observed in this age group. In consistent with this hypothesis, Hanaie et al. revealed that FA in the right superior cerebellar peduncles was positively correlated with ages from five to 14 in children with ASD but not in TD children [20]. These

findings also suggest a delayed or different time course of FA development in children with ASD compared with TD children, however, this point needs to be further investigated because of the relatively small number of children included in this study.

In summary, we investigated that microstructural integrity is correlated with age, FIQ, and VIQ in school-aged children with ASD. Therefore, we propose that the maturation of microstructural integrity of the AF is delayed in children with ASD compared to TD children and that this might be a result of altered or delayed myelination.

The limitation of this study was the limited number of children subject to the study. The large-scale study will clarify the age-dependent change of connectivity and the precise nature of AF development in children diagnosed with ASD. Moreover, this research did not utilize specified language tests. Thus, paucity of language tests which are suitable for children and validated in Japan is another obstacle in the current study, however, the development and usage of specified language tests will be employed in future studies.

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Table1.Summary of previous DTI findings about arcuate fasciculus of autism spectrum disorder

study	age	IQ	Autism number	Location	FA	MD	RD
Fletcher et al. (2010)[10] NeuroImage	14.3±1.9	PIQ>91 VIQ＞70	10	In the both AF	=	↑	↑
Lee et al. (2007) [11] Neurosci letters	16.2±6.7	IQ>85	43	In the both STG-WM	↓	NR	NR
Lange et al. (2010) [12] Autism Res	15.8±5.6 (7.0-27.8)	PIQ≧85	30	In the left SLF	↓	NR	NR
Cheng et al. (2010) [13] NeuroImage	(10-18)	IQ>80	25	In the right SLF	↑	NR	NR
Weinstein et al. (2011) [14] Human brain mapping	3.2±1.1 (1.5-5.8)	NR	22	In the left SLF	↑	NR	NR
Groen et al. (2011) [15] J Psychi Nerosci	(12-18)	IQ>80	17	In the both SLF	↓	NR	NR
Jou et al. (2011) [16] AJNR	10.9±3.7 (4.9-17.0)	NR	15	SLF	↓	NR	NR
Shukla et al. (2011) [17] J child psycho and psychi	12.8 (9-20)	PIQ>69 VIQ>71	26	SLF	↓	↑	↑
Brito et al. (2009) [31] Am Soci of Neuroimaging	9.5±1.8	NR	8	In the both SLF	=	NR	NR

Table 2 Demographic data

	Typically developing (n=11)		Autism (n=13)		Group comparison	
	MD ± SD	Range	MD ± SD	Range	F	p-Value
Age(years)	10.5 ± 2.1	7-13	9.7 ± 2.7	5-14	0.585	0.407
FSIQ	110.3 ± 8.6	99-124	104.0 ± 11.4	90-124	0.991	0.148
PIQ	110.0 ± 7.0	99-122	102.0 ± 9.9	83-114	1.832	0.035
VIQ	108.3 ± 13.7	91-129	104.0 ± 15.1	80-129	0.104	0.471
Handedness	right-handed		right-handed			
ADOS-G subscales						
Communication			3.5 ± 1.2			
Reciprocal social interaction			7.3 ± 2.6			
ASQ-J	2.5 ± 3.8					

FSIQ full scale intelligence quotient,VIQ verbal intelligence quotient,PIQ performance intelligence quotient,ADOS-G autsm diagnostic observation schedule-generic,ASQ-J Japanese version of Autism Screening Questionarie(cut off ≧13)

Table 3 Summary of each tensor parameter in the AF

|		Typically developing	Autism	p-Value
Fractional anisotropy (FA)	L	0.524±0.023	0.504±0.022	0.155
	R	0.503±0.025	0.491±0.041	0.435
Axial diffusivity (AD)	L	1.360±0.041	1.352±0.066	0.737
	R	1.369±0.041	1.351±0.051	0.361
Mean diffusivity (MD)	L	0.834±0.025	0.840±0.089	0.402
	R	0.858±0.012	0.857±0.032	0.791
Radial diffusivity (RD)	L	5.710±0.258	5.894±0.421	0.219
	R	5.966±0.216	6.067±0.425	0.461
Fiber volume	L	2245.5±453.4	2533.0±318.2	0.096
	R	2280.6±557.1	2507.4±339.8	0.252
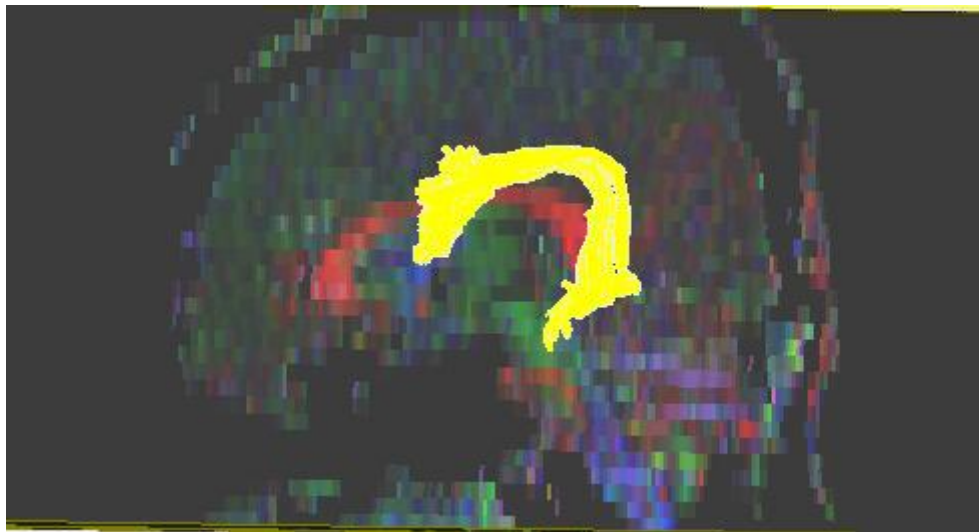
Figure1.   The reconstruction of the arcuate fasciculus.

Reconstructed tracts are shown in panel: the corps callosm = red; the arcuate
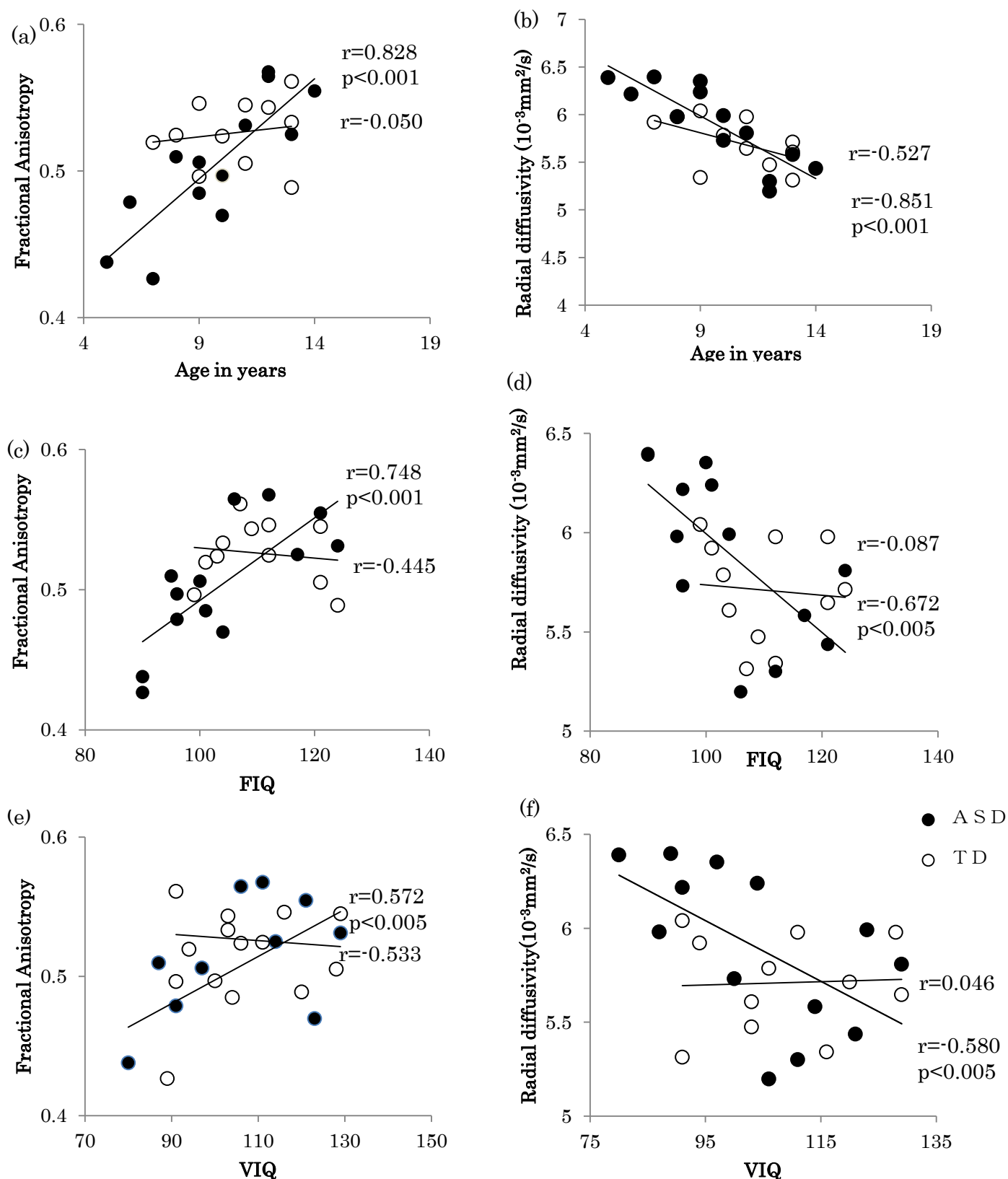
fasciculus=yellow.

Figure2.Disutribution of FA and RD relative to VIQ, FIQ, age of the arcuate fasciculus in left hemisphere.Scatter plot of the correlation analysis in the ASD and TD groups. Fraction anisotropy (FA) in the left arcuate fascicle (AF) shows a strong positive correlation with age (r=0.828, p<0.001), VIQ (r=0.572, p<0.005), and FSIQ (r=0.748, p<0.001). Radial diffusivity (RD) in the left AF shows a negative correlation with age (r=-0.851, p<0.001), FSIQ (r=-0.580, p<0.005), and VIQ ($r=-0.580$, $p < 0.005$).

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